Kidney International, Vol. 9 (1976) p. 481–488

Bicarbonate reabsorption in chronic renal failure

JOSE A. L. ARRUDA, THOMAS CARRASQUILLO, ANDREW CUBRIA, DONALD R. RADEMACHER and NEIL A. KURTZMAN

Sections of Nephrology, University of Illinois Abraham Lincoln School of Medicine and the Veterans Administration West Side Hospital, Chicago, Illinois

Bicarbonate reabsorption in chronic renal failure. Bicarbonate reabsorption was studied in dogs before and after induction of renal failure, produced by infarction of one kidney and removal of the contralateral kidney. Glomerular filtration rate and renal plasma flow decreased to 21 and 37% of control values, respectively. Fractional potassium excretion and fractional phosphate excretion increased significantly. Volume expansion resulted in a significant decrease of bicarbonate reabsorption in both control and uremic groups. At comparable levels of fractional chloride excretion, bicarbonate reabsorption was significantly higher in renal failure than in control animals. In the second group of dogs, following induction of renal failure, sodium bicarbonate was given orally in an amount sufficient to neutralize endogenous acid production. Bicarbonate reabsorption was again significantly higher than in control animals. Thyroparathyroidectomy had no effect on bicarbonate reabsorption. Absolute bicarbonate reabsorption and sodium reabsorption were linearly related in control animals and in those in renal failure; the ratio of absolute bicarbonate reabsorption/absolute sodium reabsorption was significantly higher in renal failure than in control. These data demonstrate that renal failure is associated with enhanced bicarbonate reabsorption which is not related to the state of extracellular volume, the need to increase acid excretion or the concentrations of parathyroid hormone. These findings suggest that there are additional unknown factors controlling bicarbonate reabsorption in renal failure.

Réabsorption des bicarbonates dans l'insuffisance rénale chronique. La réabsorption des bicarbonates a été étudiée chez des chiens avant et après la création d'une insuffisance rénale obtenue par l'infarcissement d'un rein et l'ablation du rein opposé. Le débit de filtration glomérulaire et le débit plasmatique rénal atteignent respectivement 21 et 37% des valeurs témoins. Les excrétions fractionnelles de potassium et de phosphate augmentent significativement. L'expansion du volume extra-cellulaire a pour conséquence une diminution significative de la réabsorption des bicarbonates à la fois chez les animaux témoins et les urémiques. A un niveau comparable d'excrétion fractionnelle du chlore, la réabsorption des bicarbonates est significativement plus grande chez les animaux urémiques que chez les témoins. Du bicarbonate de sodium a été donné par voie orale à un second groupe de chiens, après l'induction de l'insuffisance rénale, à des doses suffisantes pour neutraliser la production endogène d'acide. La réabsorption des bicarbonates, là encore, est supérieure à celle des témoins. La thyroparathyroïdectomie ne modifie pas la réabsorption des bicarbonates. Les réabsorptions absolues de bicarbonate et de sodium sont linéairement corrélées chez les témoins et au cours de l'insuffisance rénale. Le rapport réabsorption absolue de bicarbonate/réabsorption absolue de sodium est significativement plus élevé dans l'insuffisance rénale. Ces observations démontrent que l'insuffisance rénale est associée à une augmentation de la réabsorption des bicarbonates qui n'est pas liée à l'état du volume extra-cellulaire ou à la concentration d'hormone parathyroïdienne. Ces constatations suggèrent que des facteurs additionnels incorrus contrôlent la réabsorption des bicarbonates dans l'insuffisance rénale.

Received for publication October 24, 1975;
and in revised form February 2, 1976.

The factors controlling bicarbonate reabsorption in normal animals have been studied extensively in the past few years. These include the state of the extracellular volume and the concentrations of plasma potassium, plasma P_{CO_2} and parathyroid hormone (PTH) [1–5]. The renal handling of sodium, phosphate, glucose, potassium and acid excretion have been studied in detail in uremia [6–12]. Studies of HCO_3 reabsorption in uremia have yielded conflicting results. On the basis of balance studies it was suggested that some patients with renal failure waste bicarbonate [13]. Slatopolsky et al studied bicarbonate reabsorption in uremic patients under conditions of minimal volume expansion and exaggerated volume expansion [14]. They demonstrated that bicarbonate reabsorption was depressed when volume was expanded. Bicarbonate reabsorption has also been suggested to be depressed in uremic rats [15, 16]. In these studies the amount of salt in the diet was also manipulated. It was demonstrated that bicarbonate reabsorption in the uremic rat was inversely related to the state of extracellular volume. All these studies have been interpreted as showing bicarbonate reabsorption to be depressed in uremia. Based on the results of these studies, however, one is unable to determine if HCO_3 reabsorption in uremia is lower, the same or higher than that seen in normal animals with the same degree of volume expansion. Thus, the only conclusion that can be drawn from these studies is that bicarbonate reabsorption in uremia is sensitive to changes in extracellular volume. In contrast to the above-mentioned studies, Roberts et al [17] and Fillastre, Ardaillou and Richet [18] have suggested that

bicarbonate reabsorption in uremic man is either normal or increased. It seemed, therefore, appropriate to study bicarbonate reabsorption in the uremic dog and compare it to that of a normal dog with the same degree of volume expansion. Accordingly, we measured bicarbonate reabsorption in dogs before and after induction of renal failure.

Methods

Forty-two experiments were performed on 16 female mongrel dogs. The dogs were fed a normal diet containing approximately 60 mEq of NaCl per day. The dogs were anesthetized with sodium pentobarbital (30 mg/kg i.v.); light anesthesia, as judged by preservation of corneal reflexes, was maintained by subsequent small doses. An arterial catheter was used to record blood pressure and to sample blood. Arterial CO_2 tension was maintained between 35 and 45 mm Hg by appropriate manipulation of the respirator. Saline (0.9%) containing ^{125}I-iothalamate (115 μCi/liter) was administered at 0.6 ml/min throughout each experiment as a marker of glomerular filtration rate (GFR). Para-aminohippurate (PAH, 4 mg/ml in 0.9% saline) was also infused at 0.5 ml/min. $NaHCO_3$ (0.9M) was infused at varying rates to maintain a stable plasma HCO_3 concentration between 28 and 40 mEq/liter. An equilibration period of 45 to 60 min was allowed before any collection was started. Collection periods were of ten minutes' duration. Urinary and blood losses were replaced with 0.9% saline.

After two to three clearance periods, the dogs were expanded with 0.9% saline (2.5% body wt) for 30 to 60 min and further collections were obtained. The dogs were then operated on under sterile conditions. The secondary and tertiary branches of the renal artery were dissected and ligated in order to produce infarction of four-fifths of the kidney (as described by Schultze, Shapiro and Bricker [6]). One week later, the contralateral kidney was removed. A period of at least seven days was then allowed before the animals underwent the second study. The protocol used in subsequent studies was identical to that followed in the first part of the study. The following groups were studied:

Group I: In 14 dogs bicarbonate reabsorption was measured before and after induction of renal failure (uremia$_1$).

Group II: Nine experiments were performed on seven dogs with renal failure. Five of these dogs had previously been studied in group I (uremia$_1$). These animals were given 1 to 1.5 mEq/kg/day of $NaHCO_3$ orally for a period of 7 to 15 days. Two of the dogs were studied twice.

Group III: Five dogs that had been studied in group I or II underwent thyroparathyroidectomy (TPTX). Twenty-four to forty-eight hours after TPTX, bicarbonate reabsorption was again measured. TPTX was considered complete if the serum calcium concentration dropped at least 2 mg/100 ml.

GFR, blood and urinary electrolyte concentrations, PAH measurement and statistical analyses were performed as previously reported [1, 2, 4]. Comparison of the intercepts and the slope of the regression lines was performed as described by Snedcor and Cochran [19]. Results are presented as mean ± SEM.

Results

Following induction of renal failure, GFR and renal plasma flow (RPF) decreased significantly in groups I, II and III; fractional potassium excretion (FK) increased significantly in all groups. Fractional phosphate excretion increased in groups I and II and was unchanged in the TPTX dogs (Table 1). Analysis

Table 1. Baseline and clearance data in renal failure during HCO_3 loading

	GFR *ml/min*	RPF (C_{PAH}) *ml/min*	FK %	FPO_4 %	Plasma K[a] *mEq/liter*	Arterial pH[a]	Plasma HCO_3[a] *mEq/liter*	Plasma PO_4[a] *mg/100 ml*
Group I (N = 14)								
Control	58.1 ± 4.57	126.1 ± 12.47	26.8 ± 2.12	25.4 ± 2.57	3.7 ± 0.11	7.35 ± 0.01	23.8 ± 0.65	4.5 ± 0.13
	$P < 0.001$	$P < 0.001$	$P < 0.02$	$P < 0.001$	NS	NS	NS	NS
Uremia$_1$	12.8 ± 2.18	39.5 ± 6.72	89.5 ± 23.60	78.2 ± 5.86	3.6 ± 0.19	7.34 ± 0.02	21.9 ± 1.77	6.8 ± 1.32
Group II (N = 7)								
Control	58.8 ± 5.30	121.8 ± 18.20	23.3 ± 3.17	32.2 ± 3.33	3.6 ± 0.13	7.38 ± 0.01	22.4 ± 0.46	4.2 ± 0.12
	$P < 0.001$	$P < 0.001$	$P < 0.02$	$P < 0.001$	NS	NS	NS	$P < 0.05$
Uremia$_2$	12.0 ± 2.27	35.8 ± 7.28	61.8 ± 11.35	76.1 ± 5.85	3.7 ± 0.35	7.39 ± 0.02	23.9 ± 1.12	6.0 ± 0.50
Group III (N = 5)								
Control	65.8 ± 8.06	148.8 ± 18.31	31.1 ± 2.94	29.3 ± 2.61	3.4 ± 0.14	7.39 ± 0.02	22.4 ± 0.73	4.3 ± 0.25
	$P < 0.001$	$P < 0.01$	$P < 0.01$	NS	NS	NS	NS	NS
TPTX	15.1 ± 2.16	31.1 ± 3.91	54.9 ± 4.88	38.3 ± 19.01	3.3 ± 0.18	7.40 ± 0.02	24.1 ± 3.82	4.6 ± 0.42

[a] Pre-bicarbonate loading values.

of variance showed no significant difference in GFR, RPF and FK among the three groups. Plasma K and plasma HCO_3 were unchanged in renal failure (Table 1). Plasma phosphate was slightly higher in groups I and II but achieved significance only in the latter group (Table 1). There was no difference in plasma K and HCO_3 among controls, renal failure and TPTX groups.

Figure 1 plots HCO_3 reabsorption against fractional chloride excretion (FCl) for control (C) and uremia$_1$ (U_1). It can be seen that volume expansion led to a decrease in HCO_3 reabsorption in both groups. HCO_3 reabsorption was significantly higher in U_1 than in C (C, $y = 28.8 - 0.49x$, $P < 0.001$; and U_1, $y = 30.7 - 0.19x$, $P < 0.001$). Analysis of covariance showed that these two lines were significantly different. At levels of FCl comparable to those of control (0 to 12%), the regression line for U_1 is $y = 31.2 - 0.30x$; the intercept of this line is significantly higher than that of control ($P < 0.005$).

Figure 2 plots HCO_3 reabsorption against FCl for control, uremia$_2$ (U_2) and TPTX groups. Again, HCO_3 reabsorption was significantly higher in U_2 and TPTX than in control (U_2, $y = 31.7 - 0.17x$, $P < 0.001$; and TPTX, $y = 30.6 - 0.05x$, NS). The intercept and the slope of these two lines were significantly different than those of the control line (U_2 intercept and slope, $P < 0.005$) and TPTX (intercept, $P < 0.005$; and slope, $P < 0.025$). The points of U_1, U_2 and TPTX overlap; although some points of controls overlap with U_1, U_2 and TPTX, in general, the uremic and TPTX points are higher than controls (95% confidence limits do not overlap). The regression line for all points of U_1, U_2 and TPTX is $y = 31.5 - 0.23x$, $P < 0.001$. Analysis of covariance showed that this regression line was significantly different than that of control (slope, $P < 0.025$; and intercept, $P < 0.005$). Analysis of variance showed no significant difference in HCO_3 reabsorption, FCl or plasma HCO_3 among U_1, U_2 and TPTX. It is, therefore, valid to pool data of U_1, U_2 and TPTX as one single group and to compare them with the control data.

Table 2 shows a sample experiment before and after induction of chronic renal failure. Before induction of renal failure, plasma HCO_3 and HCO_3 reabsorption in control periods averaged 32.5 mEq/liter and 29.9 mEq/liter of GFR, respectively. Volume expansion resulted in an increase in FCl and GFR, and HCO_3 reabsorption decreased to a mean of 25.8 mEq/liter. In renal failure GFR decreased to approximately 25% of control levels. Mean HCO_3 reabsorption, before volume expansion, was 31.1 mEq/liter of GFR at a plasma HCO_3 concentration of 31.4 mEq/liter and FCl of 3.8%. Thus, despite a lower plasma HCO_3 concentration and higher FCl, HCO_3 reabsorption was higher in renal failure than

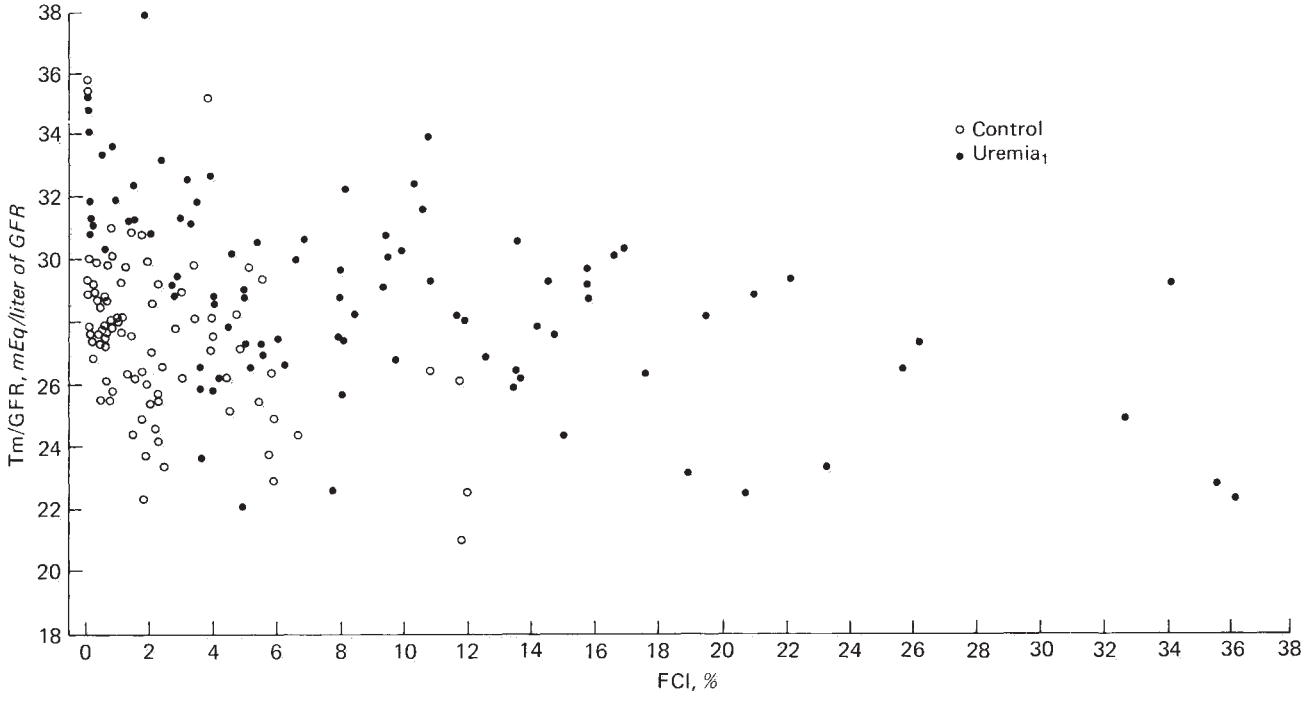

Fig. 1. *This figure plots HCO_3 reabsorption against fractional chloride excretion (FCl) in control* (open circles) *and uremia$_1$* (closed circles).

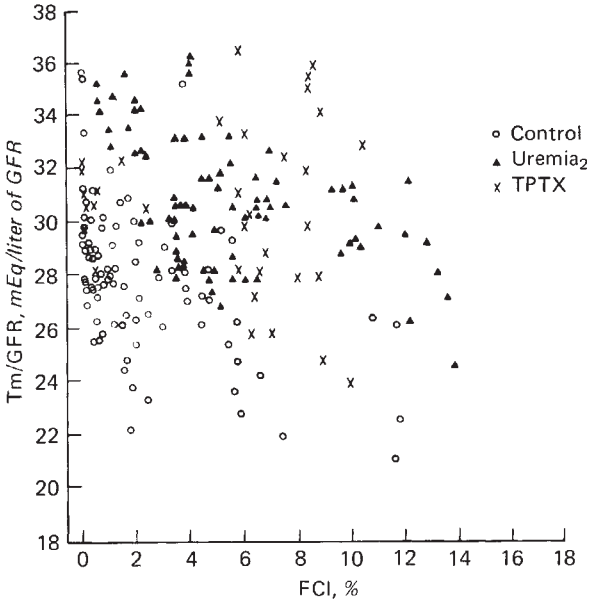

Fig. 2. *This figure depicts HCO_3 reabsorption in control* (open circles), *uremic dogs treated orally with $NaHCO_3$* (closed triangles) *and in TPTX uremic dogs (represented as x).*

in control. Volume expansion resulted in a significant increase in GFR and FCl. As can be seen HCO_3 reabsorption was higher in renal failure than in control despite comparable levels of FCl, plasma HCO_3 and plasma K concentrations.

Plasma HCO_3, plasma K, arterial pH, HCO_3 reabsorption, FCl and the ratio of absolute HCO_3 reabsorption/absolute Na reabsorption for control and uremic dogs are presented in Table 3 (the values are the mean of all periods). HCO_3 reabsorption was significantly higher in uremia than in control ($P < 0.001$), despite a significantly higher value of FCl in uremia ($P < 0.001$). Plasma HCO_3 and arterial pH were also significantly higher in uremia ($P < 0.001$). Plasma K concentrations were not different in control and uremia. Figure 3 plots absolute HCO_3 reabsorption against absolute Na reabsorption for the control and uremic groups. Absolute HCO_3 and Na reabsorption were linearly related both in control and uremia (C, $y = 54.1 + 0.18x$, $r = 0.95$, $P < 0.001$; and uremia, $y = 7.8 + 0.21x$, $r = 0.97$, $P < 0.001$). Analysis of covariance showed that the slopes and intercept of these two lines were significantly different ($P < 0.005$ and $P < 0.025$). Thus, absolute HCO_3 reabsorption per unit of Na reabsorption was greater in uremia than in control.

To eliminate volume expansion as a variable influencing HCO_3 reabsorption, the ratio of absolute HCO_3 reabsorption/absolute Na reabsorption was plotted against plasma HCO_3 in Fig. 4. As can be seen, the ratio of absolute HCO_3 reabsorption/absolute Na reabsorption increased as plasma HCO_3 increased both in control and uremia (C, $y = 0.05 + 0.004x$, $P < 0.001$; and uremia, $y = 0.11 + 0.003x$, $P < 0.001$). The 95% confidence limits of the means do not overlap (C, 0.193 – 0.179; and uremia, 0.223 – 0.209). Thus, for any given concentration of plasma HCO_3, the ratio of absolute HCO_3 reabsorption/absolute Na reabsorption was significantly higher in uremia than in control animals (Fig. 4 and Table 3).

Discussion

The renal handling of sodium, phosphate, glucose and K have been studied in detail in uremic animals and in man [6–10]. Acid excretion has also been the subject of detailed investigation in uremia [11, 12]. Despite these many studies of acid excretion, the pattern of HCO_3 reabsorption in uremia has been poorly studied. On the basis of balance studies, Schwartz et al [13] have suggested that some patients with renal failure waste HCO_3. Studies in uremic men and rats have also suggested that bicarbonate reabsorption is depressed. This depression of HCO_3 reabsorption has been attributed to extracellular volume expansion and increased concentrations of PTH [14–16, 20]. Our results may seem to contradict the findings of previous studies of bicarbonate reabsorption in uremia. These previous studies have shown *only* that HCO_3 reabsorption in uremia is sensitive to changes in the state of extracellular fluid volume. Based on these earlier studies, however, one is unable to determine whether bicarbonate reabsorption in uremia is higher, lower or the same as compared to normal subjects with the same degree of volume expansion [14–16, 20]. No attempt to eliminate volume expansion as a variable influencing bicarbonate reabsorption was made. This can be accomplished by studying bicarbonate reabsorption on the background of moderate volume expansion [2]. The effect of different maneuvers (e.g., uremia, K concentrations, etc.) on bicarbonate reabsorption can then be disclosed by comparing bicarbonate reabsorption at the same level of fractional chloride excretion and inferentially the same degree of volume expansion. Our results (Figs. 1 and 2) show that in uremic dogs, as in normal dogs, bicarbonate reabsorption decreases with volume expansion. For any given degree of volume expansion, however, bicarbonate reabsorption is higher in renal failure than in control subjects.

Another way of eliminating volume expansion as a factor affecting bicarbonate reabsorption is to compare the ratio of absolute bicarbonate reabsorption to absolute sodium reabsorption. Slaughter et al [21]

Table 2. Bicarbonate reabsorption before and after induction of chronic renal failure

	Plasma						Urine				Bicarbonate		
Time	HCO_3 *mEq/liter*	pH	P_{CO_2} *mm Hg*	Na *mEq/liter*	K *mEq/liter*	GFR *ml/min*	V *ml/min*	pH	Cl Ex *μEq/min*	FCl %	Filtered *μEq/min*	Excreted *μEq/min*	Reabsorbed *mEq/liter of GFR*
Dog 4032, weight: 12.7 kg													
0–	24.3	7.36	45.0	148	4.0								
Infuse ^{125}I-iothalamate (115 μCi/liter) at 0.5 ml/min and 0.9M $NaHCO_3$ at 1 ml/min													
60–70	31.0	7.47	44.0	153	3.4	46.0	0.5	8.00	28	0.6	1426	102	28.8
80–90	34.0	7.53	42.0	154	3.2	43.5	1.3	8.00	150	3.3	1479	208	29.2
Infuse 0.9 saline (2.5% body wt) in 60 min; continue $NaHCO_3$ at 1 ml/min													
120–130	30.1	7.52	38.0	154	3.1	54.8	2.6	7.96	356	5.8	1650	288	24.8
130–140	34.0	7.54	41.0	155	3.3	51.0	4.2	7.82	624	10.9	1734	381	26.5
140–150	33.3	7.52	42.0	154	3.2	51.4	4.8	7.77	709	11.7	1712	373	26.0
Renal failure, weight: 13.2 kg													
0–	22.0	7.32	43.0	141	3.9								
Infuse ^{125}I-iothalamate (115 μCi/liter) at 0.5 ml/min and 0.9M $NaHCO_3$ at 0.7 ml/min													
60–70	28.7	7.50	38.0	151	3.7	7.4	0.4	6.56	30	3.6	212	1	28.6
70–80	34.0	7.53	42.0	150	3.5	10.9	0.6	6.70	48	3.9	371	3	33.7
Infuse 0.9% saline (2.5% body wt) in 60 min; continue $NaHCO_3$ at 0.8 ml/min													
120–130	32.8	7.53	40.5	153	3.6	15.7	1.1	6.88	98	5.6	515	10	32.2
130–140	33.3	7.52	42.0	154	3.5	17.0	1.6	7.22	194	10.2	566	34	31.3
140–150	34.0	7.52	43.0	153	3.4	16.9	1.9	7.27	234	12.2	575	45	31.3

have demonstrated that bicarbonate reabsorption and sodium reabsorption are linearly related and suggested that the ratio of these two indexes is independent of the state of extracellular fluid volume. The current study also demonstrates that these two indexes are linearly related in both normal and uremic states. We have recently demonstrated that volume expansion over a wide range of FCl (1 to 15%) does not influence this ratio [22]. Plotting the ratio of absolute bicarbonate reabsorption to absolute sodium reabsorption against plasma bicarbonate eliminates the influence of extracellular volume on bicarbonate reabsorption and allows the evaluation of the relationship of plasma bicarbonate concentration to bicarbonate reabsorption (Fig. 4).

The ratio of absolute bicarbonate reabsorption/absolute sodium reabsorption can be derived from the linear regression of absolute bicarbonate reabsorption vs. absolute sodium reabsorption: bicarbonate reabsorption = intercept + sodium reabsorption × slope. Dividing all the terms of this equation by sodium reabsorption yields the following: bicarbonate reabsorption/sodium reabsorption = intercept/sodium reabsorption + slope. The theoretical value of this intercept is zero since in the absence of sodium reabsorption bicarbonate reabsorption will be zero or negligible; therefore, the term intercept/sodium reabsorption is equal to zero or close to zero. This means that the ratio of bicarbonate reabsorption/sodium reabsorption is dependent only on the slope of the regression line of these two indexes. In the above equation the effect of volume on the ratio is likely represented by the term intercept/sodium reabsorption which is essentially zero. Thus, large changes in sodium reabsorption do not alter the ratio bicarbonate reabsorption/sodium reabsorption. It is possible that changes in intracellular hydrogen concentration determine the slope of the above equation. Thus, changes in slope should reflect factors influencing bicarbonate reabsorption other than volume. The ratio is also independent of the urine flow because urine flow cancels out and, thus, errors in urine collection will have no influence on the calculation of this ratio. It should be pointed out, however, that this ratio is independent of the state of extracellular fluid volume during acute bicar-

Table 3. Bicarbonate reabsorption in renal failure[a]

	Arterial pH	Plasma K *mEq/liter*	Plasma HCO_3 *mEq/liter*	Tm/GFR *mEq/liter of GFR*	FCl %	Ratio HCO_3 reabsorption / Na reabsorption × 100 %
Control ($N = 16$)	7.50 ± 0.01	2.9 ± 0.07	32.4 ± 0.31	27.6 ± 0.32	2.1 ± 0.27	18.6 ± 0.32
	$P < 0.01$	NS	$P < 0.02$	$P < 0.001$	$P < 0.001$	$P < 0.001$
Uremia ($N = 26$)	7.53 ± 0.01	3.0 ± 0.09	33.6 ± 0.44	29.8 ± 0.47	7.2 ± 1.20	21.6 ± 0.35

[a] The values obtained in the 16 normal dogs during control were compared to 26 experiments in uremia in the same 16 dogs.

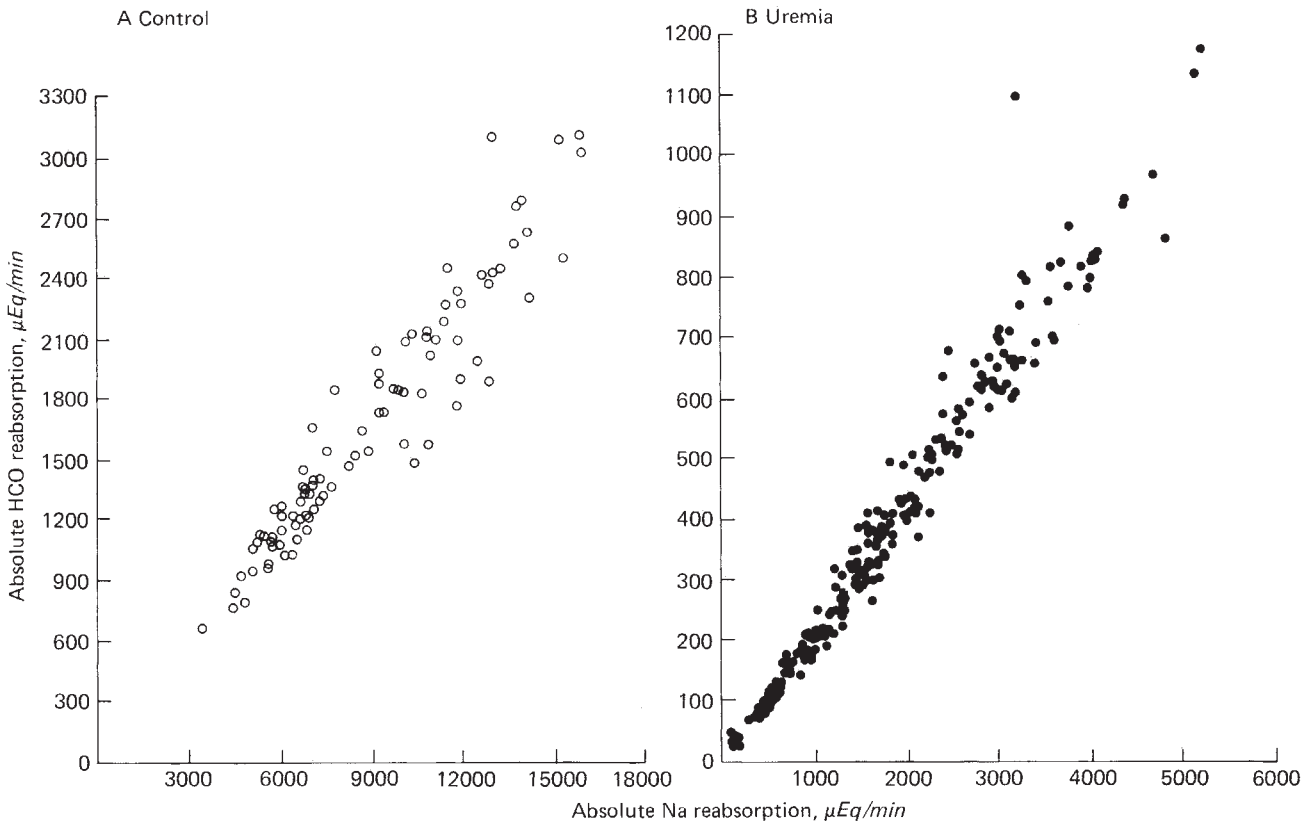

Fig. 3. *Absolute HCO_3 reabsorption is plotted against absolute Na reabsorption for normal dogs* (left panel) *and uremic dogs* (right panel).

bonate loading. In this situation volume expansion depresses both sodium bicarbonate reabsorption as well as sodium chloride reabsorption. In acid-base disturbances, such as during correction of most forms of metabolic alkalosis (FCl < 1%), volume expansion depresses sodium bicarbonate reabsorption out of proportion to its effect on sodium chloride reabsorption. Thus, the effect of volume expansion, under these conditions, on absolute bicarbonate reabsorption is more marked than the effect on absolute sodium reabsorption, which involves the sum of sodium chloride and sodium bicarbonate transport, and the ratio falls.

Our results, therefore, demonstrate that bicarbonate reabsorption in renal failure, although sensitive to changes in the state of extracellular fluid volume and plasma bicarbonate concentration, is significantly higher than in controls. These findings are in complete agreement with a recent study of bicarbonate reabsorption in the uremic dog [23]. Fillastre et al [18] studied bicarbonate reabsorption in normal and uremic man and noted that the slope of a plot of absolute bicarbonate reabsorption against GFR was higher in uremic patients than in normal subjects. They concluded that uremia leads to a disruption of glomerular tubular balance for bicarbonate. This conclusion is supported by our data. The finding of enhanced bicarbonate reabsorption in uremia suggests that there are additional factors that control bicarbonate reabsorption.

The studies by Rector, Carter and Seldin [24] and Vieira and Malnic [25] have conclusively indicated that bicarbonate reabsorption takes place through hydrogen ion secretion. Studies of acid excretion in renal failure have demonstrated that net acid excretion/unit of GFR is increased [11]. Our data show that steady state plasma bicarbonate did not change in renal failure; therefore, it is obvious that net acid excretion per nephron must have increased. One might also expect total hydrogen ion secretion per nephron (measured as bicarbonate reabsorption/unit of GFR) to be increased in renal failure. Our study confirms this prediction. Oral administration of sodium bicarbonate (in an amount sufficient to neutralize endogenous acid production and consequently sufficient to prevent the adaptive increase in net hydrogen ion secretion) failed to lower bicarbonate reabsorption in renal failure. This suggests that in

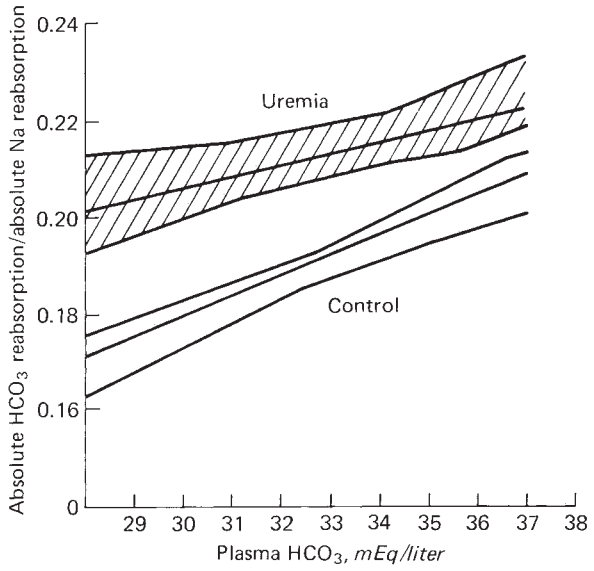

Fig. 4. *The ratio of absolute HCO_3 reabsorption/Na reabsorption is plotted against plasma HCO_3 in control and uremic animals.* The 95% confidence limits are shown.

renal failure the increased hydrogen ion secretion per nephron is not dependent on the necessity to increase net acid excretion per remaining nephron.

Parathyroid hormone administration to normal and TPTX dogs results in a depression of bicarbonate reabsorption [4, 5]. The elevated concentrations of circulating PTH, consistently found in renal failure, have been suggested to result in bicarbonate wastage [20]. In our study, bicarbonate reabsorption was high in renal failure despite the presence of secondary hyperparathyroidism. Removal of the parathyroids in normal dogs results in enhanced bicarbonate reabsorption; in our uremic dogs, TPTX did not result in any change in bicarbonate reabsorption. Thus, PTH does not seem to play an important role in bicarbonate reabsorption in this model of canine renal failure.

Severe potassium depletion is known to be associated with enhanced bicarbonate reabsorption [2]. Intracellular potassium depletion has been demonstrated recently in patients with renal failure of long duration [26]. It is, therefore, possible that intracellular potassium depletion may have been responsible for the enhanced bicarbonate reabsorption in our uremic animals. In renal failure of relatively short duration, however, one would expect intracellular potassium to be increased rather than decreased. It is highly unlikely, however, that renal failure of such short duration may have caused a sufficient degree of potassium depletion as to result in enhanced bicarbonate reabsorption. Recently it has been suggested that phosphate depletion, by decreasing intracellular hydrogen ion concentration, leads to a depression of bicarbonate reabsorption [27]. Alternatively, the high concentrations of phosphate found in renal failure could lead to an increase in bicarbonate reabsorption by elevating intracellular hydrogen concentration. It seems unlikely that the small rise in plasma phosphate observed in our uremic dogs was responsible for the enhanced bicarbonate reabsorption though further study is needed before this mechanism can be completely excluded. Schmidt, Gavellas and Bricker [23] have indicated, however, that dietary phosphate restriction in uremia does not prevent the increase in bicarbonate reabsorption.

In conclusion, bicarbonate reabsorption is high in the uremic dog. The enhanced bicarbonate reabsorption seen in uremia is not related to the state of extracellular fluid volume, the need to increase acid excretion or to the concentration of PTH. This suggests that there are unknown factors controlling bicarbonate reabsorption in uremia and requires further study. Bicarbonate reabsorption in uremic man must be reevaluated to determine if uremia enhances total hydrogen ion secretion per nephron in man as it does in the dog. As stated above the evidence available to date *only* demonstrates that bicarbonate reabsorption in the human with renal failure is sensitive to changes in extracellular fluid volume. At the present time one cannot determine if the level of bicarbonate reabsorption in uremic man is lower, the same or higher than that seen in normal man with the same degree of volume expansion. It is possible that this pattern of high bicarbonate reabsorption in the uremic dog may represent a species difference. Further studies are necessary to elucidate this point.

Reprint requests to Dr. Neil A. Kurtzman, Section of Nephrology, University of Illinois Hospital, 840 South Wood Street, Chicago, Illinois 60612, U.S.A.

References

1. KURTZMAN NA: Regulation of renal bicarbonate reabsorption by extracellular volume. *J Clin Invest* 49:586–595, 1970
2. KURTZMAN NA, WHITE MG, ROGERS PW: The effect of potassium and extracellular volume on renal bicarbonate reabsorption. *Metabolism* 22:481–492, 1973
3. KURTZMAN NA: Relationship of extracellular volume and CO_2 tension to renal bicarbonate reabsorption. *Am J Physiol* 219:1299–1304, 1970
4. KARLINSKY ML, SAGER DS, KURTZMAN NA, PILLAY VKG: Effect of parathormone and cyclic adenosine monophosphate on renal bicarbonate reabsorption. *Am J Physiol* 227:1226–1231, 1974
5. CRUMB CK, MARTINEZ-MALDONADO M, EKNOYAN G, SUKI W: Effects of volume expansion, purified parathyroid extract and calcium on renal bicarbonate absorption in the dog. *J Clin Invest* 54:1287–1293, 1974

6. SCHULTZE RG, SHAPIRO H, BRICKER NS: Studies on the control of sodium excretion in experimental uremia. *J Clin Invest* 48:869–877, 1969
7. SLATOPOLSKY E, CAGLAR S, PENNELL J, TAGGART D, CANTERBURY J, REISS E, BRICKER NS: On the pathogenesis of hyperparathyroidism in chronic renal disease. *J Clin Invest* 50:492–499, 1971
8. REISELBACH RE, SHANKEL SW, SLATOPOLSKY E, GUTOWITZ H, BRICKER NS: Glucose titration studies in patients with chronic progressive renal disease. *J Clin Invest* 46:157–163, 1967
9. SHANKEL SW, ROBSON AM, BRICKER NS: On the mechanism of the splay in the glucose titration curve in advanced experimental renal disease in the rat. *J Clin Invest* 46:164–172, 1967
10. SCHULTZE RG, TAGGART DD, SHAPIRO H, PENNELL JP, CAGLAR S, BRICKER NS: On the adaptation in potassium excretion associated with nephron reduction in the dog. *J Clin Invest* 50:1061–1068, 1971
11. DORHOUT MEES E, MACHADO J, SLATOPOLSKY E, KLAHR S, BRICKER NS: The functional adaptation of the diseased kidney to ammonium excretion. *J Clin Invest* 45:289–296, 1966
12. SELDIN DW, COLEMAN AJ, CARTER NW, RECTOR FC JR: The effect of Na_2SO_4 on urinary acidification in chronic renal disease. *J Lab Clin Med* 69:893–903, 1967
13. SCHWARTZ WB, HALL PW, HAYS RM, RELMAN AS: On the mechanism of acidosis in chronic renal disease. *J Clin Invest* 38:39–52, 1959
14. SLATOPOLSKY E, HOFFSTEN P, PUERKERSON M, BRICKER NS: On the influence of extracellular fluid volume expansion of uremia on bicarbonate reabsorption in man. *J Clin Invest* 49:988–998, 1970
15. LUBOWITZ H, PUERKERSON M, ROLF D, WEISSER F, BRICKER NS: Effect of nephron loss on proximal tubular bicarbonate reabsorption in the rat. *Am J Physiol* 220:457–461, 1971
16. ESPINEL CH: Influence of sodium excretion on bicarbonate reabsorption in experimental chronic uremia. *J Clin Invest* 56:286–291, 1975
17. ROBERTS KE, RANDALL HT, VANAMEE P, POPPELL JW: Renal mechanisms involved in bicarbonate reabsorption. *Metabolism* 5:404–418, 1956
18. FILLASTRE JP, ARDAILLOU R, RICHET G: Excretion de bicarbonates en reponse a une surcharge alcaline au cours de l'insuffisance renale chronique. *Nephron* 5:437–453, 1968
19. SNEDCOR G, COCHRAN WG: Analysis of covariance, in *Statistical Methods* (6th ed). Ames, Iowa, Iowa University Press, 1967, pp. 419–432
20. MULDOWNEY F, DONOHOE J, CARROL D, POWELL D, FREANEY RF: Parathyroid acidosis in uremia. *Q J Med* 41:321–342, 1972
21. SLAUGHTER BD, OSIECKI HS, CROSS RB, BUDTZ-OLSAR O, JEDRZEJCZY K: The regulation of bicarbonate reabsorption. *Pflügers Arch* 349:29–40, 1974
22. RADEMACHER DR, ARRUDA JAL, KURTZMAN NA: On the quantitation of HCO_3 reabsorption. *Clin Res,* in press
23. SCHMIDT RW, GAVELLAS G, BRICKER NS: The paradoxical effect of uremia on bicarbonate reabsorption in dogs. *Abs Proc Am Soc Nephrol* 7:79, 1974
24. RECTOR FC JR, CARTER NW, SELDIN DW: The mechanism of bicarbonate reabsorption in the proximal and in the distal tubules of the kidney. *J Clin Invest* 44:278–290, 1965
25. VIEIRA FC, MALNIC G: Hydrogen ion secretion by rat renal cortical tubules as studied by an antimony electrode. *Am J Physiol* 214:710–718, 1968
26. BILBREY GL, CARTER NW, WHITE MG, SCHILLING JF, KNOCHEL JP: Potassium deficiency in chronic renal failure. *Kidney Int* 4:423–430, 1973
27. GOLD LW, MASSRY SG, ARIEFF AI, COBURN JW: Renal bicarbonate wasting during phosphate depletion: A possible cause of altered acid-base homeostasis in hyperparathyroidism. *J Clin Invest* 52:2556–2561, 1973